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THE TREATMENT OF PSORIASIS WITH VITAMIN A AND TRIAMCINOLONE*

INTERIM REPORT

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THE psoriatic lesion shows characteristic histological changes in which parakeratosis of the stratum corneum and absence of the stratum granulosum are prominent features. Histological, biochemical and histochemical investigations over a wide field have gradually built up the concept that one or more enzyme system in the skin is genetically defective (Romanus, 1945 ; Ingram, 1953 and Shelley and Arthur, 1958) or becomes blocked. Tickner (1961) has given a very comprehensive review of this subject. The psoriatic stratum corneum is chemically abnormal in many respects. For instance it contains high concentrations of sulphydryl groups, (Percival and Stewart, 1930 ; Mescon and Flesch, 1952 ; Magnus, 1956; Braun-Falco, 1957 and Rhodes, Baron and Calnan, 1960), phospholipids (Snider, Gottschalk and Rothman, 1949 ; Hollander, Sommers and Grimwade, 1954 ; Braun-Falco, 1958 and Jarrett, 1958, 1960 and Jarrett and Witham, 1961), glucosamine (Flesch, Roe and Esoda, 1960) and an abnormally low amount of α-amino nitrogen (Flesch and Esoda, 1957 ; Stuepel and Szakall, 1957 and Rhodes *et al.* 1960). Although such changes may be indicative of several different enzymatic failures in psoriasis during the formation of parakeratotic stratum corneum, they have been noted in other scaly conditions. Jarrett, Spearman and Hardy (1959) regarded them as no more than by-products of the speeding up of the epidermal

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cell proliferation which is an important feature of psoriasis, but which is also present in many other skin disorders, notably in keratoses, warts and carcinoma. In support of this it was noted that the epidermis in psoriasis might be thrice the normal thickness but that this returned to normal during healing (Jarrett, and Witham, 1961). The durability and chemical and physical stability of normal keratin were lacking because insufficient time was given for the full polymerization of the polypeptide chains and for the formation of a high content of disulphide bonds.

Jarrett and Spearman (1959) investigated the effect of vitamin A on parakeratotic stratum corneum and confirmed the finding of Lawrence and Bern (1958) that this vitamin applied topically stimulated the production of a stratum granulosum in that part of the epidermis of a rat's tail where it is normally absent. They adapted this idea to the treatment of psoriasis. The vitamin A in " solubilized " form was applied to one side only in a patient receiving triamcinolone by mouth and they noted greater improvement on this side than on the control ointment side. Shelley, Harum and Pillsbury (1958) had already shown the dramatic clearing of psoriasis in patients receiving oral triamcinolone : but as is well known, the use of triamcinolone by mouth gives rise to a train of side effects so frequently that it is now used only in selected cases. No such disadvantages appear to arise from its topical application. Jarrett and Spearman therefore (1959) decided to use 0·1% triamcinolone acetonide with vitamin A in a cream base. We thought their results encouraging enough to warrant a double blind clinical trial.

Investigations.

The trial was designed to compare two ointments, " vitamin A " and " control ". The basic ointment contained 0·1% triamcinolone acetonide in a cream base. The vitamin A ointment was made by adding one part of " solubilized " vitamin A, in a concentration of 100,000 units per ml., to three parts of basic ointment. The control ointment contained one part of the vitamin A vehicle without the vitamin to three parts of basic ointment.

We compared the two ointments in cases of bilateral psoriasis and excluded cases without bilateral lesions. The patients who entered the trial had variously distributed lesions in different stages of activity and severity. They were each given two containers, the lid and container of one being labelled R and the other L, and they were instructed to apply each ointment twice daily by gentle inunction on the appropriate side. One container was filled with vitamin A ointment, the other with control ointment. The allocation of ointments to containers was by a series of random numbers.

The two ointments differed slightly in colour, one being yellowish and the other white, but the patients were not told which was expected to be effective, nor were the physicians responsible for the trial told to which side the vitamin A was being applied, nor did they see the ointments. At one stage, to check that the applications were being made correctly, the patients were sent a letter asking to which sides the yellow and white ointments were being applied. The replies, which were not seen by the physicians, showed that the trial was being carried out correctly.

Patients continued in the trial for eight weeks or until a difference was noted between the two sides. When two or more physicians saw the patient at any one visit and the differences that they noted between the sides were contradictory the result was recorded as " no difference between sides ". The criteria for assessing improvement were less scaling, or less redness. Serial photographs were also taken before and during the treatment of many of the patients.

We assessed the results sequentially. The patients were admitted to the trial as they were seen at the clinic, and as soon as a differential response was noted it was plotted (Fig. 1). When planning the trial we assumed that about 10% of the lesions would respond to the control treatment. Psoriasis is so common and so

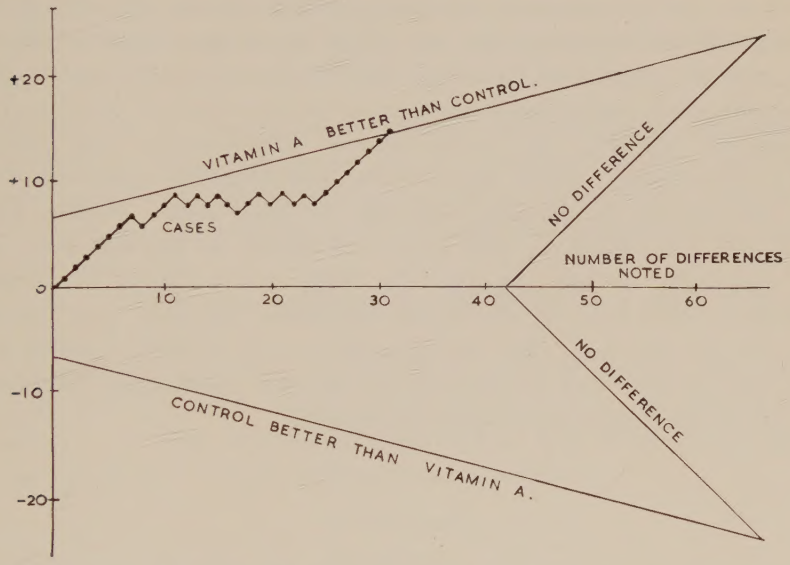

FIG. 1.—The horizontal scale marks the number of cases showing differences between sides ; the vertical scale marks the number of preferences for the vitamin A ointment less the number in favour of the control ointment.
Each spot on the curve represents a case. The trend from the outset is definitely in favour of the vitamin A ointment but this trend only achieved significance ($P > 0{\cdot}05$) with the thirty-first case when the curve crosses the upper boundary.

difficult to treat that we designed the trial to be capable of detecting a response rate of even 25%. These response rates may be entered on a chart given by Armitage (1954) which shows that the trial is required to test $\theta = 0{\cdot}75$ or $0{\cdot}25$ against the null hypothesis $\theta = 0{\cdot}5$. A closed sequential scheme was therefore adopted with $\alpha = 0{\cdot}025$, and $\beta = 0{\cdot}05$, with the boundaries given in Table 5 of Armitage's paper (1957) : see Fig. 1. The trial was terminated when the plot crossed the upper diagonal boundary, at the thirty-first case.

RESULTS.

Forty-three patients entered the trial : one patient failed to attend and another ignored the instructions : 41 remained. In 5 cases no detectable changes were seen on either side, in 5 cases there was equal improvement on both sides and in 31 cases there was greater improvement on one side than the

other. Of these 23/41 (56%) showed a more favourable response to the vitamin A ointment and 8/41 (20%) showed the reverse, viz. greater improvement on the control ointment side.

Thus the chance of improvement on vitamin A ointment is $(23+5)/41 = 0{\cdot}68$, and on the control ointment $(8+5)/41 = 0{\cdot}31$. The difference is statistically significant ($P > 0{\cdot}05$).

The trial therefore appears to establish the superiority of the vitamin A ointment over the control, in spite of the considerable response to the control ointment due perhaps partly to its triamcinolone content, but such a level of response to control treatment does not differ much from reported figures on placebo response which may be as high as 35% (Beecher, 1953 and 1956).

The lesions which responded showed great variation in their speed and degree of regression. Striking and unmistakable improvement was sometimes noticed in two weeks. Rapid improvement and complete regression attributable to the vitamin A ointment occurred in three cases. Another patient's lesions healed completely on both sides, but earlier on the side receiving the control ointment. In the majority the differences between the sides were less obvious, and some of the slight differences recorded may have been fortuitous and irrelevant. The photographs proved of some value as a check on this type of error and occasionally as evidence of changes not previously noted. They confirmed the majority of records.

Discussion.

Reduction of scaling was the most obvious first sign of improvement, and when differences had been recorded the patients were taken out of the trial. For clinical interest the sides were reversed and several showed the expected reversal of effects : but these observations could not be used for statistical analysis because the patients could easily distinguish the two ointments, and they would naturally expect the effects to be reversed after the reversal treatment. In three cases spontaneous reversal of effects was noted after several weeks, the worse side gaining on and ultimately surpassing the other. One explanation could be that the patient surreptitiously reversed the two ointments, but there are other possible reasons suggested below.

There is increasing awareness amongst clinicians of the factors in blind trials which may cause confusion in interpreting results and this trial uncovered some of them. Amongst these were :

(i) Noticeable differences between the two ointments.
(ii) Asymmetry of the lesions on the two sides of the body.
(iii) The right-handedness of most subjects which makes for unequal applications to the two sides.

(iv) Differences between lesions in their age, site, thickness, amount of scaling and dryness, which might modify their response.

(v) A positive delayed response on the control side due to a variety of possible factors (Wilkinson, 1961) such as absorption of the active drug which reaches this side by devious route ; or the psychosomatic boost which results from improvement on one side and which spills over on to the other side that is lagging behind.

(vi) The natural history of the disease with its unexplained and unpredictable waxing and waning irrespective of treatment.

(vii) The patient's failure to apply the ointments to the indicated side either continuously, or even at all.

Against the last we have been favourably impressed with the almost unfailing good faith, conscientiousness and perseverance of these patients even when improvement has been slight, and we agree with Church (1958) when he remarks on the hopeful attendance of patients with psoriasis over many long years for so little relief.

There was a considerable tendency for the lesions to relapse after several weeks in spite of treatment.

Several patients complained of burning on one side, known later to be the side treated with vitamin A. Only one patient showed an eczematous reaction in the lesions and this occurred on both sides. The inflammation subsided slowly and patch tests to both ointments were negative.

Summary.

A double blind right-against-left closed sequential trial was made to compare the effects on psoriasis of a cream containing vitamin A and triamcinolone acetonide as against a similar cream with triamcinolone alone.

Forty-one patients with bilateral psoriasis were treated.

The response to the ointment containing vitamin A and triamcinolone was significantly greater than that to the control ointment containing only the triamcinolone.

We cordially thank Dr. Ruth Porter of Messrs. Lederle (Cyanamid of Great Britain Ltd.) and Dr. Audrey Baker of Vitamins Ltd., for their co-operation and for the generous supplies respectively of triamcinolone cream with base and vitamin A with inert vehicle.

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THE TREATMENT TIME IN PSORIASIS.*

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THE credit for the development of the treatment of psoriasis with crude coal tar and ultra-violet light belongs to Goeckerman and his name will always be associated with it. While the mode of treatment which has been developed in Leeds utilizes artificial sunlight and baths, it presents such fundamental differences both in technique and in local applications that it has been identified by various authors as the Ingram treatment (Fast, 1960). Probably its most important feature is the use of dithranol in Lassar's paste in which the dithranol is much more active than in an ordinary ointment base ; this was discovered accidentally when one of our house physicians inadvertently prescribed dithranol in this form and produced a dramatic improvement in a patient who had previously been responding only slowly. The present report is an analysis of the results of 2174 courses of treatment in patients with psoriasis attending the Skin Department of the Leeds General Infirmary during the years 1958 to 1960 inclusive. It is intended that these results should serve as a base line against which other forms of treatment can be assessed. We have not tried here to assess how long the patient remains clear after stopping treatment and do not claim that we produce longer remissions than follow other forms of therapy.

METHOD OF TREATMENT.

This has been fully described previously by Prof. Ingram (1953, 1954) but is briefly recapitulated here in case some readers are unfamiliar with the details. Patients are treated either as in-patients or as out-patients depending largely on how near the hospital they live and whether they can attend the hospital daily ; in either case the treatment is the same. The patient starts with a tar bath in which he scrubs the lesions with a nail brush for ten minutes. The bath is prepared by adding 6 fluid ounces of liquor picis carbonis B.P. to a 30-gallon bath. After drying himself he is then exposed to U.V.R. from a Hanovia Alpine Sun Lamp starting with quite small doses—a quarter of a minute at 3 feet ; the dose is increased slowly but care is taken to avoid any marked erythema. Dithranol paste is then applied exactly to each patch of psoriasis and it is in the use of this paste that the most care and experience is required. It is essential that the paste should be of the right consistency and we have found from past experience that variations in the quality of the soft paraffin used to make the Lassar's paste may make a great difference in the effectiveness of the treatment. Suitable soft paraffin should have a melting point of 46° C. Our standard paste contains two grains of dithranol in one ounce of Lassar's paste (0·42%). After

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the first or subsequent applications, the skin around the plaques may become red but it is essential that the paste should only be applied to the site of the original plaque. Patients react very differently to the dithranol paste, some may become red and even blistered after one application whilst other may show no reaction at all. The strength of the paste may have to be adjusted to suit the patient and some may only be able to stand half a grain to the ounce (about 0.1%) whilst in others, particularly after a few days' treatment, the paste may be increased to 4 grains (about 0·8%) or even 6 grains (about 1·2%). The same applied to different areas of the body ; the skin under the breasts or in the groins may only be able to stand 0·1% whilst that of the hands, feet, elbows and knees may require 1·2%.

The careful application of the paste may take a long time especially in a patient with widespread small lesions ; sometimes when they are too profuse and fine the treatment is temporarily modified and a greasier paste is used containing dithranol in equal parts of Lassar's paste and soft paraffin. This is much less active and if used in 0·1% strength can be smeared all over the normal and abnormal areas without causing too much reaction. After a shorter or longer period many of the spots will have cleared with this leaving more resistant areas often over the elbows, knees, etc. which can be treated with the standard dithranol paste. When all the lesions have been treated the patient is dressed with stockinette rolls. These are prepared in various widths and pieces are cut off first of all to cover the trunk and then narrower rolls are used to form sleeves and leg pieces which are secured by tape to the trunk piece and peripherally by a band of strapping. When this dressing is finished the patient may be completely covered except for his face and neck and usually the fingers, and he is able to put on his normal clothes, if an out-paitent, and continue at his work. This routine is continued daily until the plaques seem to be clear. The local application is then changed to Ung. Hydrarg. Ammon. et Picis Carb. $\bar{c}$. Acid. Salicyl. B.N.F. in order to remove the stains of the dithranol and reveal any areas which may require further treatment. Similarly if the patient reacts too fiercely to the paste, it is replaced by the above ointment for a few days until the inflammation settles down. Whilst this is the standard treatment for the skin there are numerous minor modifications which are used occasionally for short periods such as a tar paste or, on the palms and soles, painting with crude coal tar. For the scalp a dithranol pomade of the following formula is used.

Dithranol . .	4 grains
Liquid paraffin .	360 minims
Lanette wax . .	120 grains

If reasonable care is taken there is no risk of this causing conjunctivitis. This again is replaced by a tar and mercury ointment periodically to clear away the stains of the dithranol. Occasionally Grenz-rays are given to very resistant patches and severe nail lesions are treated with small doses of x-rays.

While the local treatment is described in detail here, we must emphasize that the patient is also considered as a whole. Attacks of psoriasis are often provoked or maintained by some disability or stress either internal or external. We make every effort to uncover these and if possible to remove them. In children outbreaks often follow attacks of tonsillitis and if so, the tonsils are removed. Any anaemia, etc. is corrected. Environmental and psychological problems are gone into often with the help of the lady almoner whilst many patients get great assistance from daily contact with our nursing staff to whom they may unburden themselves whilst having their treatment. Highly strung patients are put on a sedative. The only special internal treatment which has been used in any number of patients has been injections of vitamin B_{12} and the effects of this will be discussed below. None of these patients has been put on triamcinolone or other corticosteroids by us though in some instances we have had to wean them from such treatment prescribed elsewhere.

Details of the Survey.

The results are those of all psoriasis treatment carried out in the Leeds Infirmary Skin Department for a period of approximately three years. The patients were either in-patients at this hospital or its semi-convalescent unit or attended as out-patients. Both categories attended on five days a week for treatment.

Six clinicians participated in the prescription of treatment and the assessment of results. None of them was informed of the existence of the survey until the collection of results was complete. The records of day-to-day treatment and of the final assessment and disposal were kept by the nursing staff who carried out the treatment.

The results have been analyzed in terms of courses of treatment initiated. The length of a course of treatment was estimated from when the patient first attended for his tar baths, etc. until his discharge and was measured in days, excluding Saturday and Sunday. Some patients had one or more relapses during the survey period and each course of treatment is assessed separately in the results. The outcome of the treatment has been classified as " successful " when the patient was discharged in need of no further treatment, and as " unsuccessful " when this was not achieved.

Results.

In all, 2174 courses of treatment were started during the period of the survey. In 54 of these the record was incomplete or ambiguous and these have been omitted from further consideration. Of the remaining 2120 courses, 2034 (95%) were successful. Of the 75 unsuccessful cases, 6 were admitted to other hospitals and were lost to the present survey, 15 were transferred to treatment at home and 54 either defaulted or had to terminate their treatment because of illness or pressing circumstances.

The time under treatment until discharged as " successful " is recorded for both in-patients and out-patients in the histogram Fig. 1. This shows the out-patients to have a slightly longer recovery time than the in-patients. Both groups show the peak or recoveries in the third and fourth weeks with a marked decrease over the subsequent weeks. The longest period under treatment was observed in an outpatient whose recovery required fourteen weeks.

The mean and median treatment times of the whole successful group are given in Table I. As the few patients who required an excessively long time for treatment have a disproportionate effect on the mean it is felt that the median provides a more useful indication of the effectiveness of treatment. Using this we see that for 2034 cases (the 95% of our patients in whom treatment was " successful ") the median time of clearing was 18·5 days. In-patients with 15·2 days showed rather more rapid clearing than out-patients with 19·5 days.

In a small number of patients the normal treatment had to be modified because the patient was intolerant of one of the components used. The results of these modified treatments are shown in Table II. Those who had either dithranol or tar omitted took significantly longer to recover. The group which had no U.V.R. and which consisted almost entirely of in-patients did not show a significant difference either from the in-patient group or the whole group.

Another small group had injections of vitamin B_{12} 1 mg. daily in addition

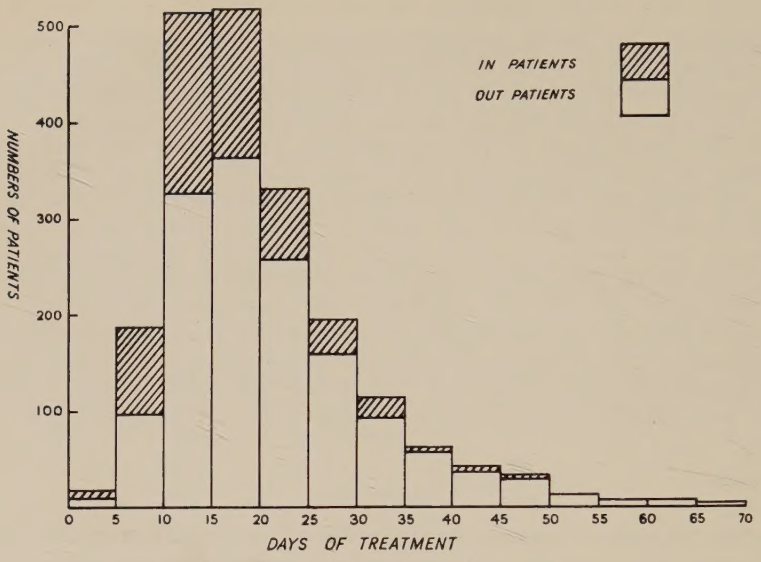

FIG. 1.

to the routine treatment. About half of these were given the injection after showing a poor response to the standard regime and were in consequence a highly selected group of poor response. No information could be gained from this group. The remaining thirty-five had vitamin B_{12} from the start of their treatment and were not selected on the basis of poor response. It is not known definitely whether there was any other basis for their selection but it seems probable that they were a random sample. The results are shown in Table III and these show no improvement over those of the whole group.

TABLE I.—*Treatment Courses Terminating Successfully.*

	Number.	Mean.	Median.
Total	2034	$19 \cdot 9 \pm 0 \cdot 17$	$18 \cdot 5$
Inpatient	584	$16 \cdot 5 \pm 0 \cdot 23$	$15 \cdot 2$
Outpatient	1450	$23 \cdot 8 \pm 0 \cdot 27$	$19 \cdot 5$

TABLE II.—*Results of Treatment with One Component Omitted.*

	Number.	Mean.
Tar	10	$30 \cdot 7$
Dithranol	29	$27 \cdot 3$
U.V.R.	12	$16 \cdot 6$

TABLE III.—*Results when Vit. B_{12} was Added.*

Number	Mean	Median
35	$21 \cdot 4 \pm 1 \cdot 8$	$18 \cdot 7$

Discussion.

We have been able to find very little accurate information in the literature about the time taken to clear patients with psoriasis. Goeckerman (1931) makes no mention of it in his original articles. Ormsby and Montgomery (1954) say that " with Goeckerman treatment the patient is relieved in two to four weeks ". Sulzberger (1942) describes a modified form of this treatment suitable for out-patients which require " 4 to 8 weeks in most cases ". More detailed results are given by Ellis *et al.* (1948) following the use of liquor carbonis detergens, and U.V.R. ; 13 of their 16 patients completely cleared during periods of two and a half weeks and fifteen weeks whilst 24 who were treated with the solution alone faired rather worse. A careful analysis of the effect of various types of treatment over the years 1943 to 1958 is given by Huriez (1958) and his average period of hospitalization over this time is 57 days. None of the above results can compare with the present series in which 95% of the patients were successfully treated in a median time of 18·5 days. The results with in-patients (15·2 days) were somewhat better than with out-patients (19·5 days). It seems reasonable to expect that a patient resting in hospital would respond more rapidly than one going about his ordinary work. Some of the difference, however, may be due to a tendency to discharge in-patients slightly earlier than out-patients, owing partly to pressure on beds and partly to the patient's desire to get back to work. The results with out-patients are probably the more dramatic for they show that it is possible for a patient to get his psoriasis cleared up whilst he is continuing his daily work if he is prepared to devote about an hour a day for three weeks to treatment.

In the small group in which one ingredient of treatment had to be left out, the importance of both the tar and the dithranol is clearly seen. Although the number which were treated with U.V.R. was only 12 and is not statistically significant, the results suggest that U.V.R. may not materially affect the speed of clearing. Even if this were true, and we do not accept it on these figures, we would still feel that U.V.R. is important as it may play a part in delaying relapses. One of us has shown (Hellier, 1940) that the incidence of psoriasis was decreased during those winters which followed summers with a high total of sunshine and the same may apply to treatment with artificial sunlight.

Finally we would emphasize that this is not a treatment which can be handed out casually to any patient ; it can only be carried out properly in a department which is well organized with baths, artificial sunlight and local applications, all under the direct control of the dermatologist. Results such as ours can only be obtained by the most careful attention to detail and the devotion of a well-trained nursing staff.

Summary.

The time required to clear patients with psoriasis is analyzed on the basis of 2174 courses of treatment.

Ninety-five per cent of those with complete records (2120) were successfully treated.

The median time for all patients was 18·5 days, that for in-patients being 15·2 days and for out-patients 19·5 days.

Evidence is presented that vitamin B_{12} has no influence on the speed of response.

We would like to acknowledge our indebtedness to Professor Ingram who built up the organization for treating psoriasis in Leeds, some of whose patients are included here ; also to Dr. S. T. Anning for access to his cases. Above all we wish to thank Sister McCutcheon and her staff on whose care and devotion so much of the success of this treatment depends.

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NAPKIN PSORIASIS.*

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DURING the past seven years we have collected a series of twenty-eight cases of a characteristic eruption in infants which is most marked in the napkin area and has many of the features of psoriasis.

The cases occurred in 12 boys and 16 girls. The average age of onset was eight weeks ; 6 began in the first 1–2 weeks and 3 began in the 6th–8th months. In 3 there was a history of psoriasis in a parent and in 7 a history of eczema in a parent. Two of the patients were twins. The infants were normal at birth and most were breast fed. The eruption began in the napkin area in 19 cases. In 7 it started in the scalp but involved the napkin area within a few days, and in 2 the scalp and napkin areas were simultaneously affected.

The eruption was explosive in nature, usually reaching its maximum in a few days, although in 8 cases lesions continued to erupt for some weeks, particularly on the trunk. It consisted of yellowish-brown patches with, in places, superimposed scales. The edge was well defined and figurate and normal skin was sometimes visible amongst the affected patches (Figs. 1, 2, and 3). In the napkin area the lesions were large and in the distribution of maximum contact with the napkin as in the usual napkin erythema (Fig. 4). On the trunk the patches were smaller and irregularly scattered. The eruption in the scalp varied from a few circumscribed patches to widespread lesions, but in all cases a well marked edge could be seen in some areas and patches of normal skin ran up to and were enclosed by the eruption. In one case the lesions were confined to one side of the scalp. In 12 cases there was some eruption in other sites ; on the face in 2, in the axillae in 2, round the ears and neck in 4, and in more than one of the sites in 4. There was slight weeping from small areas of the eruptions in 4 cases. Itching was not a feature and most babies made no attempt to scratch and rub. Their general health did not appear to be affected. In answer to direct questioning 6 out of 12 mothers had noticed the smell of ammonia from the napkins.

Mycological investigations were carried out in 17 patients and in the napkin area *Candida albicans* was present in 4 cases. In 10 of these patients scrapings were examined from the scalp and trunk lesions but candida was not found in any including 3 cases in whom it had been present in the napkin area. One case in which *Candida albicans* was found relapsed after three weeks and at this time scrapings failed to demonstrate the presence of fungi.

A biopsy from the eruption in the napkin area showed moderate hyperkeratosis, parakeratosis and a well marked lymphocytic infiltration in the upper corium, extending into the rete and forming focal collections in its substance.

All cases were treated with bland applications. In most this consisted of zinc paste and aqueous emulsifying ointment in equal parts to the napkin area and at the same time routine advice was given, as in the usual napkin eruption. A calamine ointment

* Based on a paper read at the Annual Meeting of the British Association of Dermatology at Liverpool in July 1961.

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was used on the trunk lesion and a tar, mercury and salicylic acid ointment on the scalp.

The eruption settled down in 4–8 weeks in 4 cases, in 2–4 months in 14 cases, and 10 cases took 4–6 months to clear. Two cases, which cleared up, later relapsed, but again responded to treatment. All except one have been followed up, but in only 5 for over 4 years. No cases have developed more typical psoriasis at a later date, 4 have since had occasional eczematous patches and 5 continued with intermittent eruptions in the napkin area.

Discussion.

Scrapings from the napkin area showed *Candida albicans* in 4 cases, but in none could it be demonstrated in the scalp or trunk lesions. To evaluate the part played by monilia in these cases we tried to discover the incidence of monilial infection in common napkin rashes and took cultures from a series of children attending routine infant welfare clinics. We examined 30 children with simple and usually mild napkin rashes, in many cases of which the mothers had noticed the smell of ammonia from the napkins. Nine showed *Candida albicans* whereas none of the 30 normal controls had a positive culture. One of the control infants later developed a napkin rash and then showed *Candida albicans*. These findings strongly support the view that the monilia in the 4 positive cases was a secondary invader and of no aetiological significance. In addition Bound (1956) reported the recovery of *Candida albicans* from the napkin area in two cases of seborrhoeic dermatitis and Wachowick (1929) showed monilia was more commonly associated with psoriasis than with normal skin.

The condition described is probably closely related to seborrhoeic eczema. In seven cases there was a history of eczema in a parent ; 4 cases had some weeping and 4 cases later developed minor eczematous eruptions. However, against this diagnosis are the appearance of eruption, particularly the well defined edges in all areas, the lack of itching, the close relationship to napkin irritation and involvement of areas in contact with the napkins rather than flexures, the explosive onset and the relatively quick resolution. A simple napkin erythema in a child with a tendency to develop seborrhoeic eczema might explain the condition but the appearance of the eruption is much more in keeping with a diagnosis of psoriasis. It would be tempting to suggest that these infants had a constitutional psoriatic tendency and that the eruption was precipitated by the napkin irritation. We have no evidence of this as none of the cases followed up so far have developed psoriasis. However they have hardly had time to do so as conventional psoriasis is unusual in early childhood. Out of 1274 cases of psoriasis seen at one hospital in Bristol in the past 10 years, only 5 occurred before the age of 3. Apart from its involvement of the napkin area, this eruption seen in an adult would unhesitatingly be diagnosed by most dermatologists as psoriasis or perhaps flexural psoriasis. We suggest that the cases we have described have a similar relationship to seborrhoeic eczema as flexural psoriasis has to seborrhoeic eczema in the adult.

Fig. 1.

Fig. 3.

Fig. 2.

Fig. 4.

Warren and Faulkner.

It is difficult to give the condition a suitable label. There have been a number of these cases described in the literature under various titles. Tachau (1924) used the term " psoriasoid ", suggested to him by Jadassohn. " Psoriasiform seborrhoeid " and " seborrhoeiform psoriasis " are terms which have been used but neither stress the factor of irritation by the napkin. Perlman (1960) refers to the condition as " seborrhoeic diaper reaction," and Swift (1960) as " diaper dermatitis with psoriasiform lesions." It is a difficult condition to name and the term " napkin psoriasis " may not be accepted. However it seems clear that a condition exists which has features which make it difficult to place under the generally accepted term of " seborrhoeic eczema ".

In the lively discussion which followed presentation of this paper most agreed that the condition was an entity. Some held that monilia played a part in spite of what was considered overwhelming evidence against this. Others agreed that the condition had many of the features of psoriasis. The fact that none of the cases had later developed conventional psoriasis was considered to be against the diagnosis but it was pointed out that the cases had not been followed for long enough for this to have occurred. Also, psoriasis in infancy is usually much more difficult to cure than most of the cases of the " napkin psoriasis " type seen by members at the meeting. Many thought that the condition was closely related to seborrhoeic eczema.

Summary.

Twenty-eight infants are described who had a characteristic eruption, usually starting in the areas in contact with the napkin, but rapidly affecting the scalp and in many cases the trunk. In all areas the lesions had a well demarcated and often polycyclic edge giving the appearance of psoriasis. *Candida albicans* were isolated from the napkin area in four cases but not from lesions elsewhere. *Candida albicans* can readily colonize simple napkin eruptions and it is considered that the fungus did not play a primary role in these four cases. Although there are certain features in common with seborrhoeic dermatitis the condition was more closely related to psoriasis. The eruption cleared up in 2–4 months with the use of bland applications. None of the infants has developed psoriasis since but only five have been followed for more than four years.

We would like to express our thanks to Dr. C. D. Evans for referring cases to us and for his continued help ; also to Miss Mary English for carrying out the mycological investigations. We are also indebted to Dr. Harold Lee, of Genatosan Ltd., for financial help in publishing the coloured plate.

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THE INFLUENCE OF SOAP ON THE PERMEABILITY OF THE EPIDERMIS.*

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The demonstration *in vitro* that soap increases the permeability of the human epidermis to water (Bettley and Donoghue, 1960) naturally raises the question whether this increase of permeability is also in respect of substances other than water. Most previous studies into this question have concerned *in vivo* measurements (Szakall, 1958) or *in vitro* techniques with full thickness skin (Blank and Gould, 1959). Since, however, the main barrier against penetration is well recognized to lie in the epidermis, it has seemed best to use isolated epidermis so as to avoid the unknown and variable factors which the dermis may contribute.

Investigation.

Method.

For this purpose an apparatus has been designed and made of Perspex (Fig. 1). It consists essentially of two halves, each of which is a flat cylinder 20 mm. in diameter and 5 mm. in depth. One face of the cylinder has a circular aperture 8 mm. in diameter. When the apparatus is assembled the two apertures lie opposite each other and are separated by a piece of epidermis (*E*) which is inserted as the two halves are opposed. These are then clamped together by the four brass screws at the corners.

After assembly, each chamber can be filled and emptied with a Pasteur pipette through a hole at the top which is closed by a Perspex stopper. In filling the chamber an air bubble is left at the top. The complete assembly is then rotated about its centre like a wheel at a speed of about four revolutions per minute throughout the period of the experiment. As it rotates, the air bubble is carried round from the top by the partial septum (*S*) until, after about one third of a revolution, it is released and rushes again to the top of the chamber.

This release of the bubble, and the resulting turbulence of the fluid, keeps the contents of the chamber effectively stirred without imposing any mechanical strain on the epidermis. In some experiments, in which it is desired to ensure that no notable change in pressure occurs between the two chambers, the stoppers may be replaced by a coiled polythene tube in which a mercury bead serves to indicate any movement of pressure.

The chamber thus filled contains about 1·5 ml. A solution of the substance to be examined is placed in one chamber with isotonic saline in the other. The appearance of the substance in the saline solution is then measured after an appropriate period in the presence and in the absence of soap and is an index of the permeability of the epidermis to that substance under various conditions.

This apparatus has certain useful features : First, the quantity of solution available, 1·5 ml., is ample for chemical assay ; second, this quantity of liquid is brought into

* Based on a paper read at the Annual Meeting of the British Association of Dermatology in Liverpool, July, 1961.

contact with a relatively large area of epidermis, i.e. about 0·5 cm.^{2}; third, a point of great importance, the liquids are kept constantly stirred.

With this technique epidermal permeability to glucose and salicylate, and the effect of soap upon this, has been measured. Epidermal permeability to soap itself has also been investigated. All these experiments have been made with skin obtained at autopsy from near the midline of the upper abdomen, the epidermis being separated by the method previously detailed (Bettley and Donoghue, 1960).

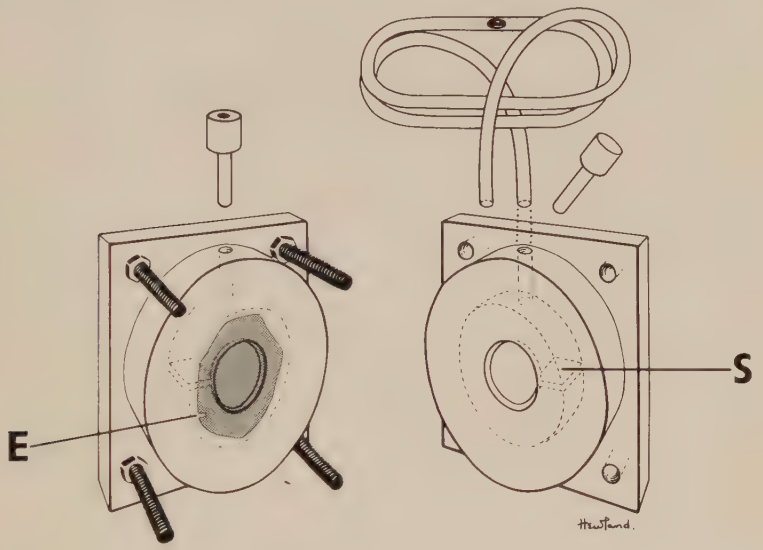

FIG. 1.

Sodium Salicylate.

For the study of the penetration of sodium salicylate, a solution was prepared containing 2·46 g./100 ml., this being about iso-osmotic. In the opposite chamber was placed isotonic saline. After one week the fluids in both chambers were removed and their salicylate content estimated. Fresh solutions were then placed in the chambers with the same epidermis for a further week and then their salicylate content again determined. This was repeated a third week.

These experiments were then repeated with the same solutions to which potassium palmitate was added to make a concentration of 1% (0·034 M). Each of these experiments normally lasted three weeks, the apparatus being assembled with epidermis and only the solutions changed. In many experiments the first week was carried through without soap in order to make sure that the epidermis was behaving normally and soap solutions used in subsequent weeks.

The experiments were carried out at room temperature, about 22° C. Salicylate estimations were carried out using 0·2 ml. of solution by the method described by King (1951).

Results.—At the end of the first week the saline showed a salicylate content varying from 0 to 18 mg. %, average 5·5. This represents the actual passage of 0 to 270μg, average 82·5 μg. for the week. The second week samples gave salicylate contents of 1·2 to 14 mg. %, average 5·8. Four experiments which were continued to the third week and two to the fourth gave averages of 2·8 and 3·0 mg. % respectively.

In the presence of soap this passage of salicylate was markedly increased. After one week the salicylate content of the sample ranged from 24 to 68 mg. %, average

45 mg. This represents the actual passage of an average of 675 μg. in the week. In the second weeks permeability of the epidermis was still greater, giving figures from 74 to 86 mg. %, average 79·8 mg. In the third week this was further increased from 108 to 132 mg. %, average 119 mg. These results are charted in Fig. 2.

It will be seen that in the absence of soap (lower curve), penetration of sodium salicylate proceeds at a very low rate, showing no increase in later weeks. The apparent tendency to reduced permeability in the third and fourth weeks is not significant. In the presence of soap (upper curve) the epidermis becomes more permeable and this change is progressive over the three weeks of the experiment.

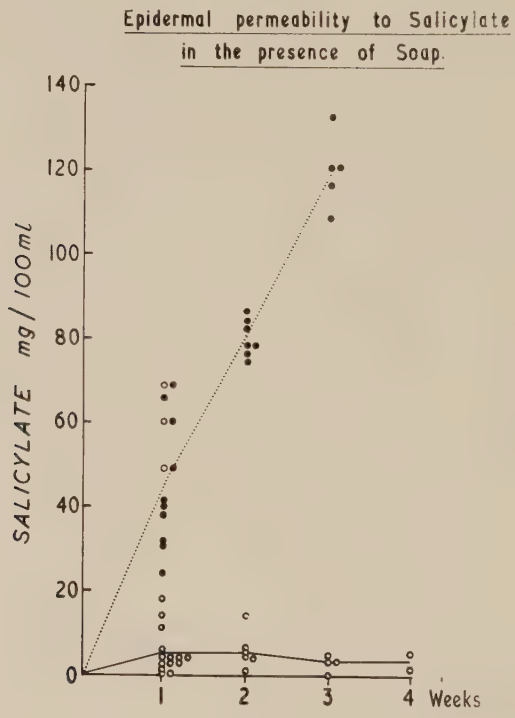

Fig. 2.

Glucose.

A solution was made of 200 mg. % of glucose in normal saline. This was placed in one chamber with normal saline on the opposite side. The glucose content of both chambers was estimated at intervals of a week or occasionally less. At first, in these experiments, unexpectedly low figures were obtained, the concentration of glucose in that chamber being much reduced. This was thought to be due to the presence of glycolytic enzymes in the epidermis and in later experiments N/100 sodium fluoride was added to all solutions. In spite of this a few experiments had to be discarded when unexpected disappearance of glucose from the chamber indicated that glycolysis had taken place.

Potassium palmitate 1% was added to these solutions and the experiments carried through in the same way as with salicylate at room temperature.

For glucose estimation 0·625 ml. of the chamber contents was diluted to 25 ml. with saturated benzoic acid solution and filtered : 1 ml. of this filtrate was used for glucose

estimation by the colorimetric method of King (1951) with arsenomolybdic acid reagent, using a photoelectric colorimeter.

Results.—In most experiments the amount of glucose passing across the epidermis in the absence of soap was extremely small, barely if at all outside the margin of error in estimation. This did not alter over a period of three weeks.

In the presence of soap the epidermis became more permeable to glucose (Fig. 3, upper curve). After the first week the saline was found to contain glucose in a concentration ranging from 0 to 33 mg. %, average 11·4 mg. %. After the second week

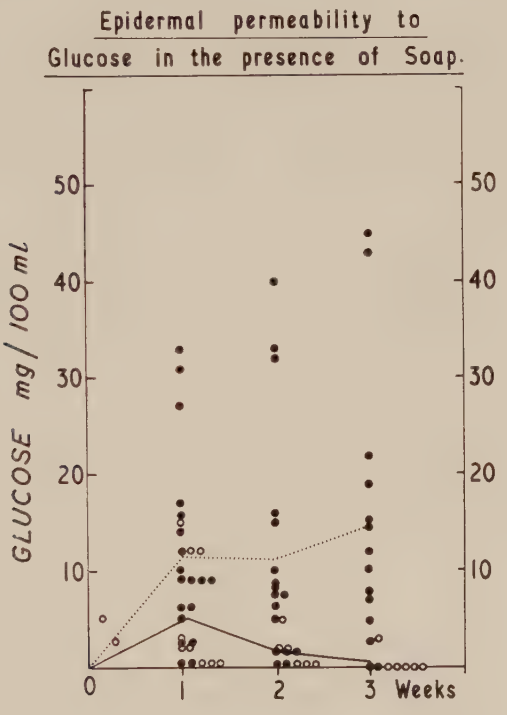

Fig. 3.

glucose content ranged from 0 to 40 mg. % but the average remained at 11·3. During the third week glucose concentration reached 0 to 45 mg. %, average 15·1. Although, therefore, the permeability of the epidermis to glucose did not rise as sharply as was seen with salicylate, there was nevertheless a more free penetration of glucose in the third week than in the first. The actual quantity of glucose which passed the epidermal barrier during the test period is not to be compared strictly with the figures obtained for salicylate since the original concentration of the salicylate solution was very much greater than that of the glucose.

Soap.

Since the chemical estimation of soap presented some difficulty, it was decided to use for this study a soap labelled with a radioactive isotope. For this purpose oleic acid labelled with ^{131}I was obtained and from this the potassium soap prepared.

In one series of experiments this potassium oleate was used in a strength of 0·2 M (about 6·4%) and in another 0·04 M (about 1·3%). The pH of the 0·2 M soap was 9·8.

Soap solution was placed in one chamber with normal saline on the other side. The solutions were sampled at intervals, their radioactivity measured and the samples replaced, so that in all these experiments the soap and saline solutions were left unchanged throughout.

Results.—All the experiments showed a permeability to soap which increased with the passage of time.

With 0·04 M soap it was possible to show some soap in the saline within four days in all cases. At the end of 26 days, when the longest experiments were concluded, the epidermis remained intact to naked-eye examination but showed, especially in three cases, considerable transmission of soap even reaching over one third of the concentration of the original soap solution.

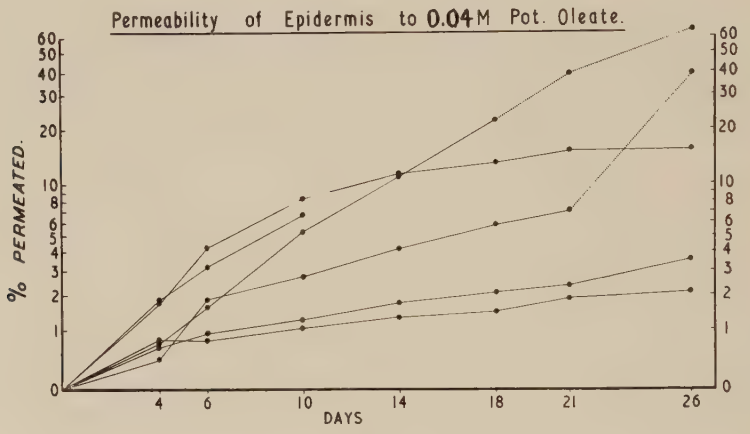

Fig. 4.

In Fig. 4 these resuls are shown against a logarithmic scale in order to set out the lower values more clearly. Since the strength of the soap solution could be expected to fall during the course of the experiment, the concentration of soap which appeared in the saline solution is here shown as a percentage of the concentration of the remaining soap solution. Thus, on the fourth day the soap found in the saline ranging from 0·42% to 1·83% represents a concentration of from 5·39 to 23·46 mg./100 ml., i.e. the quantity of soap which had actually traversed the epidermis was about 80 to 352 μg., an average of 201·9 μg. By the sixth day this quantity had reached 174 to 804 μg., averaging 537·5 μg. This indicates an increased rate of movement, since the amount of soap having crossed the epidermis in the last two days was considerably more than the total of the first four days.

With 0·2 M soap solution there was a greater absolute quantity of soap passed, but up to the tenth day this was only in proportion to the greater strength of the original soap solution (Fig. 5). When estimated on the 17th day three samples were found to have equalized with the opposite chamber and in the remaining three experiments the same was found on the 24th day.

This attainment of equilibrium probably results from a more complete breakdown of the epidermis since this was found, when the apparatus was dismantled, to be soggy and very friable.

Discussion.

Valette (1954) mentions that in alcoholic solution sodium salicylate has been stated to penetrate the epidermis, but the present results indicate that in aqueous solution it has a low penetration. This is indeed to be expected from an electrolyte which is freely soluble in water and sparingly soluble in fat solvents. Studies of the penetration of salicylic acid and its esters are not relevant since these are fat-soluble substances.

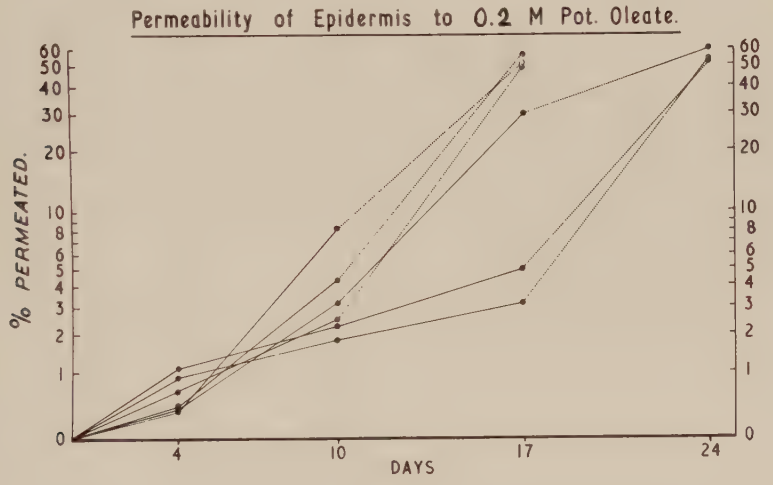

Fig. 5.

Glucose was found by Treherne (1956) to penetrate very little through rabbit's skin and the present experiments confirm this for human epidermis. This also conforms to the general rule that penetration of the intact epidermal barrier depends in part upon solubility : fat-soluble substances penetrate more readily, water-soluble substances do not.

Previous experiments (Bettley and Donoghue, 1960) have shown that ordinary soap and potassium palmitate alter the epidermal barrier and make it more permeable to water. The present experiments indicate that in the presence of potassium palmitate it becomes more permeable also to sodium salicylate and to glucose. In some later experiments not detailed here, it has been ascertained that potassium oleate has a comparable effect in respect of epidermal permeability to water and sodium salicylate. It has now been shown that potassium oleate itself probably penetrates the epidermal barrier. This involves the assumption that the radioactive iodine remains attached to the soap molecule throughout the experiments. Blank and Gould (1959) using entirely different methods have shown that sodium laurate also penetrates this barrier.

The relative permeability of these substances in the presence of soap increases with the passage of time, presumably indicating that the effect of soap continues to be exerted over a period of at least two or three weeks.

On general considerations it seems unlikely that soap will penetrate the intact epidermal barrier in any degree and that the penetration shown in these experiments results from the damage which soap itself inflicts on the epidermis. This supposition is borne out by the observation that the passage of soap accelerates as does that of salicylate and glucose.

Summary.

An apparatus is described for the measurement of epidermal permeability.

In the presence of soap, the permeability of isolated human epidermis to sodium salicylate and to glucose is increased.

Potassium oleate also penetrates this epidermal barrier.

It seems likely that these effects of soap occur because soap attacks the epidermal barrier zone.

I am much indebted to Mr. Roger Ekins for guidance and help in isotope experiments ; also to Mr. E. Dowsett for making the apparatus, and to Miss E. Hewland for the illustrations.

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THE ARCHITECTURE OF BASAL-CELL CARCINOMA.

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THERE have been few attempts to demonstrate in three dimensions the shape of tumour masses in basal-cell carcinoma. Petersen (1902), Madsen (1941) and Foot (1947) have constructed models from the magnified outlines of serial sections of specimens. This process is laborious, the model is only an approximation to the true shape of the tumour and does not show it in relation to all the normal structures around it. Petersen used vertical sections of 25 or 30μ thickness and the shaded line drawings which illustrate his article show one tumour to be superficial (model 2), another to be penetrating rather more deeply (model 1) and the third (model 4) represents only the margin of the tumour in detail. Madsen made two models of superficial tumours from sections 20μ thick cut in a horizontal plane. Foot also made two models of small, " early " lesions, using sections 6 μ thick. Each of these authors made important contributions to our knowledge of the architecture of basal-cell carcinoma. However, the picture is far from complete and a more direct method of examination than the one they used seems desirable.

Leach (1952) described a technique for cutting and staining thick sections of the skin. The advantages of this method and some of the features seen in normal skin have been discussed in a previous report (Sanderson and Thiede, 1961). In the present paper the appearance of a basal-cell carcinoma cut in 500 μ sections is described. Additional information on the origin of the neoplasm and its relationship to the stroma has been obtained from split-skin preparations of five other superficial basal-cell carcinomata.

MATERIAL AND METHODS.

The six specimens used were of tumours excised completely with a rim of normal skin. The tumour cut in thick sections was 2·5 cm. in diameter and the ellipse of skin containing it measured 5 cm. by 3·5 cm. The specimen was fixed in neutral formol-saline and divided by removing a central piece about 0·5 cm. wide for sectioning in the normal manner. The two remaining pieces were stored in formol-saline for several months and then embedded in celloidin (Mallinckrodt " Parlodion "), cut into 500 μ sections and stained with anthracene blue by the method of Leach. The procedure is given in detail in a previous report (Sanderson and Thiede, 1961). One of the two pieces was cut vertical to the skin surface and the other parallel to it. The latter sections were somewhat oblique at their edge because the skin had shrunk and curled during fixation and storage.

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The sections were examined with a stereoscopic microscope (Watson plate microscope) with magnifications of 12·5, 25, and 50 diameters. Photomicrographs were made with a monocular system using objectives of 33 mm., 16 mm., and 8 mm. nominal focal length.

A topographical plan of the piece cut in vertical sections was drawn on graph paper as follows. The length of the epidermal surface of each section of the series was measured and plotted against the thickness (0·5 mm.), the scale being 0·1 inch to 0·5 mm. Within the outline of the whole specimen, the margin of the tumour and the situation of pilosebaceous follicles were plotted by direct measurement of their position in each of the sections. Oblique hair follicles were followed through several sections and their position plotted where they pierced the epidermis.

Five specimens of small basal-cell carcinomata excised from two other patients were split into epidermal and dermal portions. The skin was macerated in 1% acetic acid for 12 to 18 hours. The layers were separated with mounted needles on a dissecting microscope using oblique incident illumination. After separation the tissues were fixed in 70% ethanol, stained with 0·005% aqueous haematoxylin (Harris) for 15 to 60 minutes and blued in tap water. They were examined with incident or transmitted light under water with a stereoscopic microscope. The clinical details of the two patients are given later.

The Thick Section Specimen.

Case I.—(Mr. Ronald Hunter's patient.) A man aged 71 years, had noticed skin tumours for more than 30 years but had not sought treatment previously. He had been a farmer and fruit-grower in South Australia and had used sheep-dip and arsenate of lead sprays for many years. Five tumours were found when his skin was examined. One on the lower abdomen measured 15 cm. across and another in the right pectoral region was 12·5 cm. in diameter. These were extensively and deeply ulcerated. The other tumours were over the right deltoid muscle (5 cm. diameter), on the scalp, and on the lower part of the back (2·5 cm. diameter each). All the tumours were excised and the one from the back was chosen to be cut in thick sections. It was a round plaque, somewhat raised above the level of the surrounding skin, indurated and translucent. It had been present for at least ten years.

The histological sections stained with haematoxylin and eosin showed a basal-cell carcinoma arranged in small solid masses and strands, and connected to the epidermis in places by pedicles (Fig. 1). The tumour did not penetrate deeply into the dermis and was surrounded by a chronic inflammatory reaction, predominantly lymphocytic. Some of the tumour masses contained melanin granules. There was a well marked palisading of the marginal cells of the tumour and a few mitotic figures were found. The epidermis over the tumour was thinned and flattened, but at the margin it was more deeply ridged and more pigmented than normal.

It is easier to describe and understand the findings if the periphery of the tumour is assumed to be of more recent origin than the centre, as seems justifiable.

The marginal epidermis.—Outside the edge of the tumour the epidermis shows changes similar to those which have been described by Madsen (1941) and Willis (1945). The rete ridges extend more deeply into the dermis than normal, and their apices are sharp rather than rounded. They do not seem to be increased in number but are wider at the base and thus compress and appear to lengthen the dermal papillae. The pigmentation of the basal layer is increased mainly at the apices of the ridges. The superficial layers of the epidermis do not seem to be affected by these changes. There is a mild cellular infiltrate in the papillary part of the dermis.

The edge of the tumour.—The proliferating cells whose increased staining marks the edge of the tumour arise chiefly from the tips of the rete ridges. A small bulbous expansion replaces the sharp apex and very soon a constriction appears between the outgrowth and the parent epidermis. The buds may originate from a series of points along the ridge. Adjacent ones seem to fuse a little distance beneath the epidermis. In this manner the papillary processes of the dermis are compressed and distorted and nodules of tumour are attached to the epidermis by several pedicles between which run tunnels of connective tissue. In some

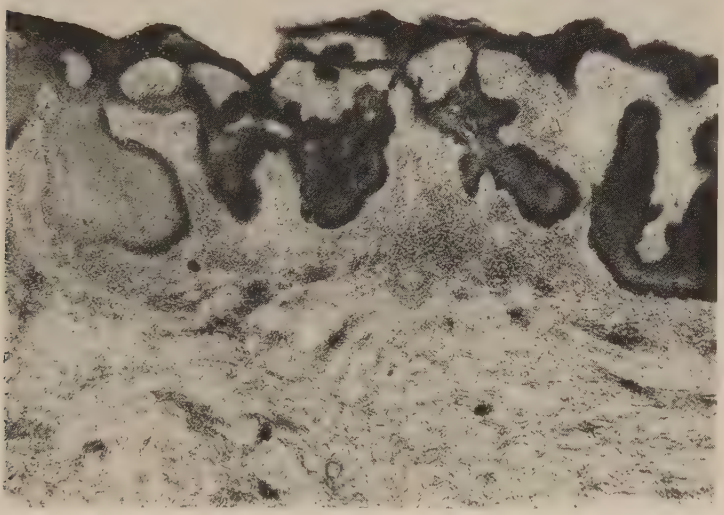

Fig. 1.

areas the growth seems to arise as a continuous expansion of a number of ridges and it extends into the dermis in a honeycomb fashion. The epidermis over the tumour loses its rete ridges and becomes flattened except where the pedicles attach to it. There are many pedicles near the margin but they become much less frequent towards the centre. This suggests that as the tumour grows down into the dermis its superficial parts regress. The connective tissue around the marginal growth is heavily infiltrated with cells which form a layer limited below by the reticular collagen of the dermis.

Patterns of growth in the centre.—Three main patterns can be distinguished. The first is produced by expanding solid masses whose boundaries are composed of palisaded columnar cells. The second consists of thin strands and sheets of cells which invade the surrounding tissue. The third is the result of piecemeal enclosure of the adjacent connective tissue by outgrowths of the tumour.

Expansive tumour masses.—At their simplest these comprise an array of spherical or ovoid units suspended from the epidermis like a string of Chinese lanterns (Fig. 2). Pure spherical forms may also occur in the deeper parts of the tumour but only rarely. Modification of the spherical outline is produced by budding from points on the surface. A single bud may grow to produce a dumbell shaped unit : multiple buds give the appearance of a mulberry (Fig. 3). Still further enlargement of the buds compresses the intervening stroma into thin septa. The outline of the resulting masses is often spherical and they are composed of a varying number of lobes like segments of an orange which are

Fig. 2.

united at the centre or the upper pole of the unit (Fig. 4). In some instances lobulation seems to be produced by the tumour growing around a blood vessel. The vessel persists and can be seen running in the depth of the septum. These expansive masses are invariably bordered by palisaded columnar cells (Fig. 11, inset). The stroma immediately adjacent to the palisade and in the interlobular septa is more translucent than the normal connective tissue and in it there are fine fibrils which run parallel to the surface of the masses. I will call this " fibrillar stroma " in the descriptions that follow.

Invading strands and membranes.—The extent of these structures and the complexity of the pattern they produce is difficult to imagine from thin sections. They are composed of elongated cells whose axes are in the line of penetration. The strands are two or three cells thick and vary in width from a thin cord to a wide ribbon or sheet. They often branch and may then diverge, but in places the branches reunite after a short distance producing a fenestrated membrane.

The course they run is a series of smooth curves. The surface of a wide membrane may form complicated undulations as it passes around masses and through the connective tissue. The strands arise directly from the epidermis in places, and in the vertical sections they are seen to curve as they pass down and to run be-

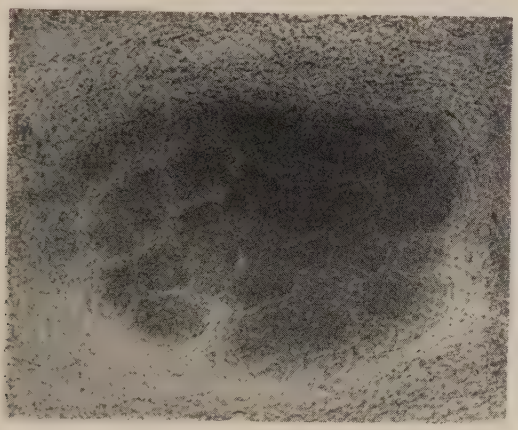

FIG. 3.

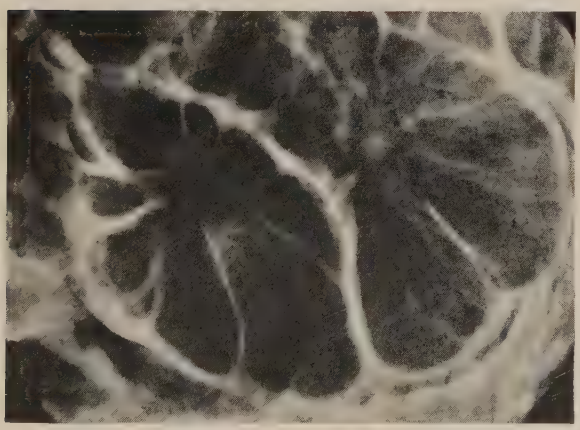

FIG. 4.

tween the rounded tumour masses and the inflammatory infiltrate in the dermis. Strands can also be seen to extend out radially from a sweat duct in one place, and to pass like fins into the connective tissue around it. Mostly, however, they come from expansive masses. At the point of origin the palisade parts at an acute angle from which the cells of the strand appear to be extruded like a school of small fish swimming through a narrow opening. The strands then skirt around adjacent masses or pass out into the connective tissue (Fig. 5). In

the latter case, secondary expansive masses may bud from one or both surfaces of a membrane of tumour. These buds are often attached by one or several narrow pedicles. Their surface is composed of a palisade of cells and may be

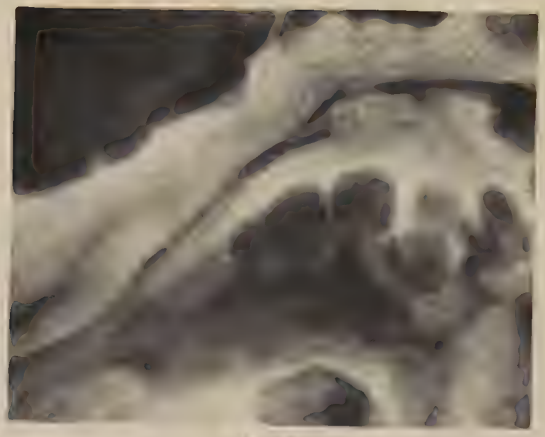

Fig. 5.

Fig. 6.

smoothly rounded or scalloped. Where secondary budding is prominent a very complex pattern results (Fig. 6). The strands may be up to several millimetres long. The connective tissue around them is not rarefied or fibrillar. It is impossible to see what determines the course they take through the connective

tissue, or what factors induce secondary budding. It seems likely that irregular elongated expansive masses may develop initially from strands. Close examination of the centre of such masses shows a core of fusiform cells lying in their long axis and in places these cells continue as a strand which issues from the end of the mass.

Piecemeal enclosure of connective tissue.—As the dominant method of tumour extension, this pattern is seen only in a few places in the specimen examined. As a minor method, however, it occurs very frequently. For instance, not all the buds that develop from a mass or membrane have a completely convex

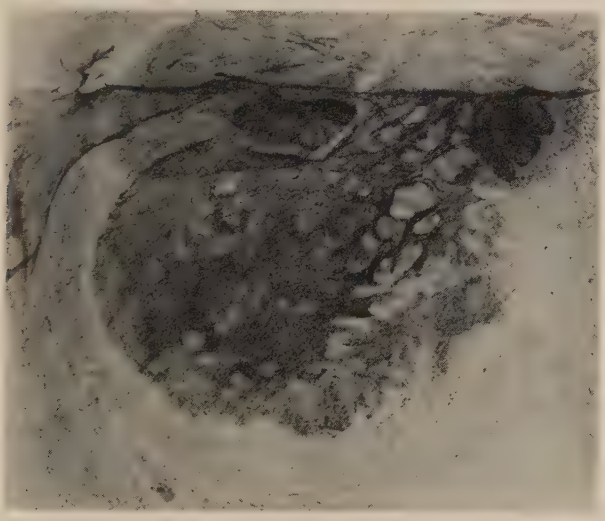

Fig. 7.

outline. Some have a dent at their outer pole which may be so deep as to produce a cup-shaped form. The lip of the cup tends to grow over the opening and thus nip off a portion of connective tissue. Quite long invaginations of stroma tissue can be seen in some of the expansive masses and it is to be assumed that these are produced in a similar fashion.

In some areas a rounded mass has the appearance of a sponge (Fig. 7, drawing). The advancing edge of this formation is composed of a honeycomb of short strands infiltrating the connective tissue. In the mass shown in Fig. 7 the edge is partly rounded and lined by a palisade of cells and partly infiltrating. The connective tissue which is being enclosed retains its fibrillar character at first, but deeper in the mass more or less spherical cavities occur whose contents are amorphous. These cavities appear to be the last evidence of portions of enclosed connective tissue after they have become completely surrounded by the tumour cells.

Close inspection of many of the apparently solid tumour masses shows that they are traversed by canals of varying lengths and calibre, often having a circular cross section. These usually communicate with the stroma at one or more points and occasionally some of the fine fibrils which run parallel to the surface of the mass can be seen to run into them. The finest of these canals are of the dimensions of blood capillaries. It is likely that they also are formed by enclosure of strands of connective tissue.

Secondary changes within the tumour.—The appearances described so far can be attributed to proliferation of the tumour and alteration in its relationship with the stroma. However, the decreasing number of pedicles connecting the

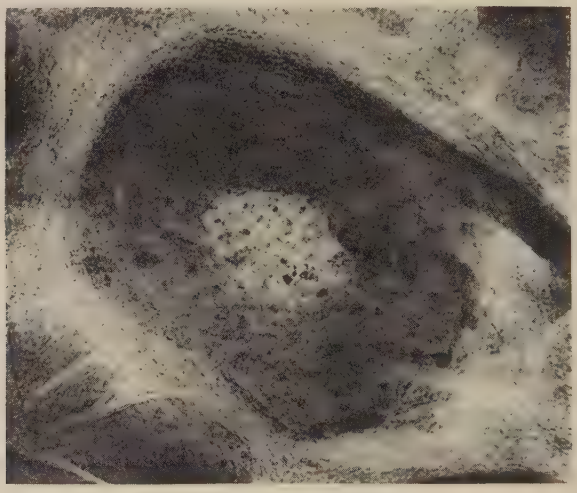

Fig. 8.

tumour to the epidermis at the inner part of the tumour compared with the marginal part has been noted. This is taken to indicate that as the tumour grows down into the dermis its superficial parts degenerate.

In some of the rounded masses a central cavity is found. The central mass in Fig. 2 shows this, and it is a striking feature in Fig. 8. Examination of the boundary between the tumour and the cavity with a higher power objective shows that flattened tumour cells, many without nuclei, are being shed into the cavity. It would seem that necrosis of the centre of the tumour is one of the mechanisms that produces these cavities. As well as cellular debris, agglomerations of pigment granules can be seen within some of the cavities. These have the characteristic form of melanophores. When the cavities occur in spherical or ovoid masses they usually have the same shape, but may not be quite central. In irregularly shaped masses they tend to follow the external contour in a smoothly curved and simplified form, e.g. pear shaped. Only a minority of

masses are excavated in this manner. Those affected are mainly the larger and more central ones. However no direct relationship can be found between the size of the masses and the tendency to cavity formation, and the thickness of the tumour tissue around the hole varies greatly from one place to another. A margin of palisaded cells is seen at the outer edge of all such cystic masses.

A somewhat similar change occurs at the skin surface in a number of places. A bowl-shaped depression is bounded at its rim by epidermis and beneath by

Fig. 9.

tumour masses and connective tissue. The bowl is filled with a thick lamellated crust of what seems to be keratinous material. This is in fact a hemispherical ulcer above a tumour mass which is attached to the epidermis by its edges.

The Involvement of Skin Appendages.

Evidence will be presented later to show that the number of pilosebaceous follicles per unit area is the same within the field of the tumour as in the surrounding skin. The basal-cell carcinoma involves the follicle chiefly by direct extension from an epidermal origin on to the wall of the pilosebaceous duct. At first this is usually asymmetrical (Fig. 9) but as the growth penetrates deeper it tends to

encircle the duct and hair follicle. The function of the follicle is not affected by encirclement of its distal part, for hairs can be found growing from a follicle whose duct is embedded in tumour 1–2 mm. thick. The sebaceous glands are less hardy and usually disappear when the upper half of the follicle is enveloped by tumour. In two places a thin-walled keratinized cyst has formed at the site of the sebaceous gland, but this phenomenon is not uncommon in normal skin (Sanderson and Thiede, 1961). In some horizontal sections the remains of a hair follicle can be identified in a tumour mass as a keratinizing tube containing a hair shaft. This structure would be unrecognizable if the hair shaft were missing.

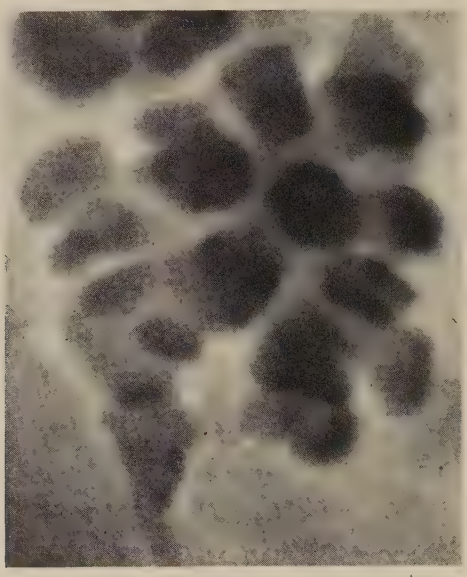

Fig. 10.

Sweat ducts are involved in several different ways. In one place membranes of basal-cell carcinoma arise from a portion of a duct, and extend radially into the surrounding dermis. Elsewhere, emerging sweat ducts can be seen to terminate in expansive masses of tumour. In the instance illustrated (Fig. 10) the mass is composed of radiating stubby digitations which, if seen in a thin section, would resemble Willis' illustration of basal-cell carcinoma in sweat glands (cf. Fig. 109, Willis, 1960). Strands of tumour may spread through the dermis to encircle sweat ducts or, more rarely, hair follicles. This process is best seen in the horizontal sections. The appendages are at first insulated from the tumour by a cuff of connective tissue, but this is later dissolved and the structures become engulfed by the growth.

Close to the tumour a considerable number of sweat ducts end blindly in

thin-walled dilatations, like bubbles blown at the end of a glass tube (Fig. 11). These sacs are either just beneath the under-surface of the tumour or in the connective tissue between masses. Similar dilatations have been produced by Lobitz, Holyoke and Brophy (1956) by surgical interruption of sweat ducts. The same type of saccular dilatation is seen in a few sweat ducts in normal skin (Leach, 1952 ; Sanderson and Thiede, 1961).

Pigmentation.—Melanin can be distinguished in three forms. There are dust-like particles in the cytoplasm of the basal cells of the normal epidermis. In the stroma and in some areas within the tumour there are small aggregations

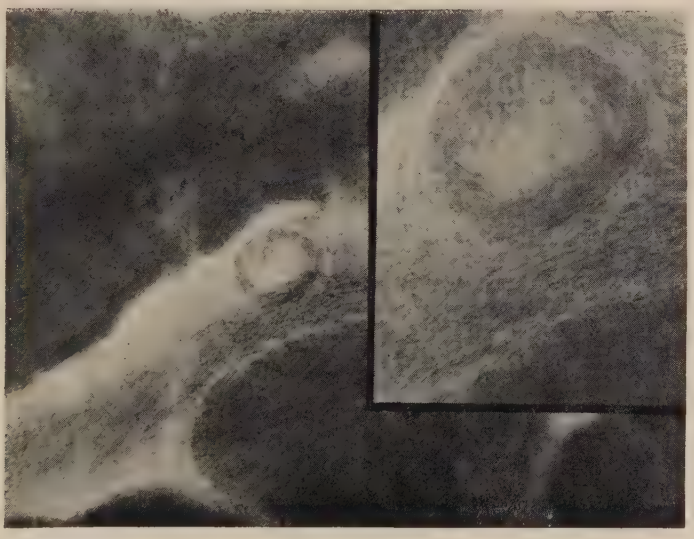

Fig. 11.

of coarse granules, which resemble the appearance of melanin within macrophages. In some tumour masses it is possible to identify dendritic cells (melanocytes) which contain fine melanin granules, but these can only be seen with an 8 mm. objective. No melanin is visible in the tumour cells, which is not surprising in view of the scanty cytoplasm that these cells possess.

The general distribution of melanin within the tumour masses is quite haphazard. For instance, in an area where the growth is mainly in the form of pedunculated masses, one of these may contain melanin whilst those adjacent do not (Fig. 2). A large lobulated complex may have an abundance of pigment in several lobes and none in the others (Fig. 4). The dendritic melanocytes are rather more numerous near the margin of a mass than at the centre and so is the finely dispersed melanin in the dendrites. Melanophores, on the other hand, tend to congregate in the centre of masses, particularly in those which are cystic, though some may be seen lying between the tumour cells within the body

of the tumour (Fig. 8). In some places the only melanin within a tumour mass is in melanophores dotted in the central region. The melanocytes which produced the melanin seem to have disappeared as the masses enlarged. Melanophores are present in the stroma around pigmented tumour masses and at the margin of the tumour.

Isolated outgrowths from pilosebaceous follicles.—A proportion of the hair follicles examined, whether within or outside the tumour areas, show a peculiar

Fig. 12.

proliferation arising from their outer surfaces. These are deeply stained rounded bodies enclosed by a capsule of rather dense fibrous tissue. They arise either from the pilosebaceous duct as in Fig. 12 or from the outer root sheath of the follicle. Nearly half of them come from the region of the hair bulb. The parenchyma of the outgrowth is composed of arborizing filaments and strands. These are often curved or branched near their outer end. They are lined by cuboidal or columnar cells, sandwiched between which may be a layer or two of flattened cells. None of the cords show any suggestion of cystic change within them. In appearance they can best be likened to the head of Medusa. Some of them are pedunculated but those in the hair bulb region arise from the whole circum-

ference of the follicle. They do not seem to be related to any particular phase of the hair growth cycle, nor does their presence necessarily interfere with the function of the follicle. Indeed the majority of follicles involved in this way possess normal sebaceous glands and have produced hair shafts even when the hair bulb is obscured by the proliferation.

The distribution of normal hair follicles and those with outgrowths was plotted on a topographical plan of the piece of skin cut in vertical sections. The density of all follicles in the skin around the tumour was 32 per sq. cm. and in the tumour area 33 per sq. cm. More than half the follicles in the skin around the tumour possessed outgrowths, but only four of twenty-one follicles within the tumour area showed them.

Split-Skin Preparations.

Case 2.—(Dr. Hugh Wallace's patient.) A woman aged 43 years had been aware of a red scaly patch on her lower back for 8 years. It was 2 by 1·2 cm. in extent, situated over the spine of the third lumbar vertebra, and had a number of small translucent papules set in it. The lesion was excised by Mr. R. J. V. Battle. Sections showed buds of basal-cell carcinoma arising from the epidermis. They were bounded by cells arranged in a palisade and were situated in the papillary part of the dermis.

Case 3.—(Dr. Hugh Wallace's patient.) A man aged 55, who had lived in the tropics for many years, had noticed tumours of the skin of his trunk for ten years. Examination showed eight tumours on the upper part of his trunk and one on his face. There was also atrophy of the skin such as follows excessive exposure to sunlight, and he had several keratoses on his back. The tumour of his face was treated by radiotherapy after the diagnosis of basal-cell carcinoma had been confirmed microscopically. The lesions of the trunk were all translucent plaques less than 1 cm. in diameter. They were excised. Four were sectioned for histological examination, and the other four were macerated whole in acetic acid. The histological picture of the four sectioned was similar. They were all basal-cell carcinomata arising from the epidermis and consisting of palisaded tumour masses that did not invade beyond the upper third of the dermis.

The appearance of the underside of the epidermis of the specimen from Case 2 is illustrated in Fig. 13. At the edge of the lesion small irregular nodules of tumour develop from the tips of the interpapillary ridges. The nodules are pierced by slender channels. Nearer the centre of the lesion the connections of the nodules with the epidermis are less numerous and extensive and the nodules themselves are larger. All the masses arising from the epidermis have smooth rounded contours and have separated quite cleanly from the dermis. There is no increase in pigmentation in or around the tumour.

The dermal component of the specimen shows the reverse process. The tumour masses have eroded into the connective tissue producing a series of impressions of the nodules. The connective tissue processes which had filled the cavities in the nodules are slender and round or flattened in section. They point in towards the centre of the tumour mass showing that the tumour has expanded laterally as it has grown down.

The four specimens from Case 3 are very similar. In each there is a central area of epidermal atrophy. This corresponds to a somewhat tumid area on the surface of the dermis. When this is explored with a sharp needle it is found to consist of a fine tough membrane (looking like lens cleaning tissue) beneath which the material is soft and friable, quite unlike normal dermal connective tissue. This soft white layer can be lifted out of its connective tissue matrix rather easily and some of the fragments have the same shape as the lobules of the expansive masses seen in the thick sections. It is evident that in the area of epidermal atrophy the growth has penetated more deeply into the dermis

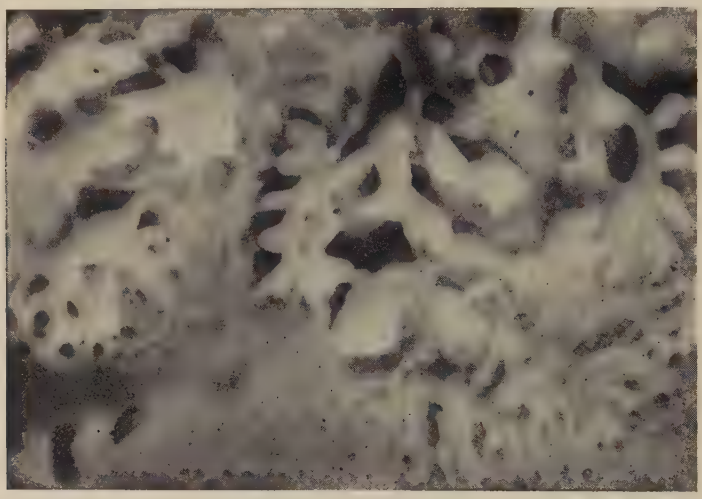

Fig. 13.

(or has originated from one of the appendages), spread out expansively, and developed around itself a fine membranous stroma from which it can be separated with ease.

The epidermal origin of the growth is also apparent in these four specimens and has the same pattern in most areas. At the periphery of the tumours proper, multiple nodules arise from the tips of the rete ridges. In some places these have the same form as the nodules shown in Fig. 13. A true punctate multifocal origin is found in several other areas. Here tiny buds of tumour, whose diameter approximates to the width of the epidermal ridges, can be seen coming from the epidermis (Fig. 14, indicated by arrows).

The epidermal origin is not particularly prominent where sweat or pilosebaceous ducts emerge, although in one or two places the latter structures are involved in contiguity. Only the distal part of the ducts of the appendages has separated and thus these preparations give no data on the relationship of the intradermal growth to appendages.

Discussion.

The thick sections and split-skin preparations on which the observations have been made do not show the fine details of cell structure and therefore cannot provide direct evidence of the histogenesis of the tumours. However, the findings suggest that much of the disagreement on the subject that is found in the literature is due to an over-sophisticated approach to the problems of cell differentiation. For instance, it does not seem necessary to seek a specific resemblance between the palisaded cells of the margin of the tumour and those of the primitive foetal follicle, the epidermal basal cells or the lining cells of the outer root sheath. When detail is reduced to bare cell outlines in the solid

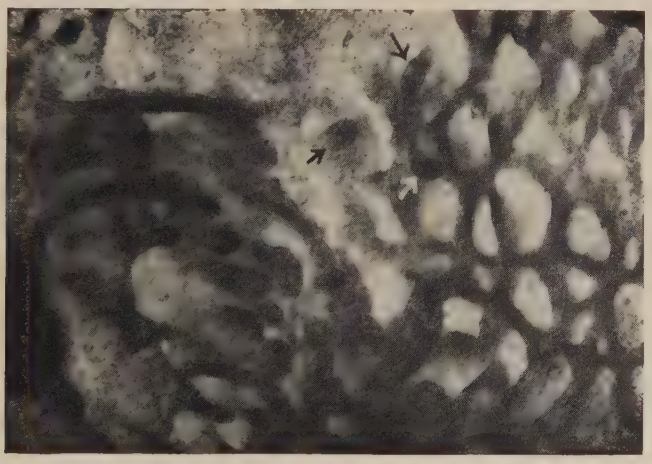

Fig. 14.

form of the masses, all these are seen to be alike in presenting a stable surface to opposed connective tissue. Within the masses the persistence of remnants of adnexal structures may give a false impression of differentiation of tumour cells, as may enclosure and alteration of the stroma. Thin strands of cells are most often in the form of sheets whose contours indicate that they are invading connective tissue planes and not attempting to differentiate into ducts or other structures. The final decision on points such as these must be made on histological and cytological data. It is clearly better to interpret histological preparations in the light of the observed behaviour of the tumour in three dimensions than through an hypothesis of the nature of tumours. The hypothesis which Cohnheim (1889) put forward tentatively (and which is now generally discarded by pathologists, see Willis, 1960) that " . . . the real cause of the subsequent tumour is to be sought in a fault or irregularity of the embryonic rudiment " has been used to support many of the interpretations of cell behaviour in basal-cell carcinoma and has been the cause of much confusion.

The tumours used in this study were all more or less superficial. The patient who provided the thick-section specimen had four other tumours, two of them very large and deeply ulcerated. The aetiological importance of arsenic in his case is questionable as he had no other stigma of chronic arsenical poisoning. The natural history of his lesions suggests that if a superficial plaque-like tumour is left long enough it will become a deeply invasive rodent ulcer. Case 2 is an example of a solitary superficial basal-cell carcinoma. The tumours in Case 3 developed in skin damaged by excessive sunburning, which also showed chronic atrophy but very little tendency to produce keratoses or squamous carcinoma. There was no history of exposure to arsenic in this case.

The material does not represent the rodent ulcer or nodular basal-cell carcinoma, which are the commonest clinical forms. It may seem unjustifiable, therefore, to draw general conclusions from the observations. It would certainly be an error to do so if there were a number of quite distinct types of basal-cell carcinoma. However many pathologists believe that detailed subdivision of this group is not possible. Willis (1960), Evans (1956) and Lund (1957) take this view on the basis of histological findings. Lennox and Wells (1951) do so after a statistical analysis of the distribution of several histological features in a series of tumours whose clinical behaviour was known. Thackeray (1951), after comparing the prognosis of treated tumours subdivided on various histological grounds, finds that only the pattern of growth is important. The prognosis is better with circumscribed tumours than with those which were mainly infiltrative. Even Lever (1948) who has proposed a detailed classification of these tumours admits that the features on which he builds the classification often occur in combination in individual lesions. This fact makes Lever's classification unworkable in practice and is good evidence against the existence of the groups he describes. If it can be assumed that basal-cell carcinoma is essentially a homogenous group of tumours, it is reasonable to postulate that the basic patterns of growth will be similar. It is, of course, very likely that a larger series of specimens would show other more complex patterns than those found in my material.

Origin of the tumour.—In his review of the literature up to 1941, Madsen recorded the almost unanimous view that superficial basal-cell carcinoma arose from multiple centres in the basal-cell region of the epidermis and its appendages. He did not hold this view himself and regarded the extension of the growth as due to an invasion through the rete ridges by cells arising from a single area. Since then the writings of Willis (1945) and Foot (1947) have given further support to the multicentric hypothesis and to the concept of the progressive conversion of normal to neoplastic cells within a field of growth rather than invasion of normal areas of the epidermis by malignant cells spreading out from a small single focus. The findings recorded here agree with these views. In one split preparation, discrete multicentric buds of new growth have been found.

The thick sections also indicate that multiple buds are the first change in the marginal epidermis and that as they invade the dermis they may coalesce and lose most of their connections with the epidermis. In the tumours I examined, this budding arises from wide areas of the epidermis, though only from the tips of the rete ridges. It is not confined to " . . . the neighbourhood of the debouchment of the hair sheaths and sweat ducts through the epidermis " as was the case in Foot's specimens. The appendages are involved mainly in the central deeper part of the growth. The complexity of the pattern here and the retrogression of the superficial part of the tumour make it impossible to decide whether this is due to extension down from the epidermis, or to foci arising *de novo* from the appendages. It is probable that both processes occur. Some writers, e.g. Dubreuilh and Auché (1901), Haythorn (1931) and Gates *et al.* (1943) have denied that basal-cell carcinoma arises from sweat glands, but the evidence of the thick sections is definite on this point.

Architecture and patterns of growth.—The manner in which the tumour spreads, the gross form of the masses and actual shape of the tumour cells appear to be due more to influences in the stroma and surrounding connective tissue than to the innate potentialities of the tumour cell. My data give no indication of the part played by the connective tissue in inducing the malignant change. The prime importance of this factor would seem, however, to be a logical consequence of the " field of growth " concept. Once the tumour masses have developed, the presence of the palisaded margin is of great significance. The palisade is always associated with rounded masses and with relative rarefaction and fibril formation in the adjacent connective tissue. It points to a stable relationship between tumour and stroma, in which the expansive force of the tumour is almost balanced by the resistance of the connective tissue reaction. Where this resistance varies from place to place the shape of the tumour masses is irregular, which is perhaps best exemplified by the fissure produced in a mass by a vessel obstructing its expansion. In places where the connective tissue defences have been breached, invasive strands of tumour spread between the fibres. The surface of these strands may subsequently be the source of fresh rounded masses. Within a small area, therefore, the tumour cells may be columnar in the palisade, almost devoid of cytoplasm within the mass and fusiform in the strands ; this variation in form depends only on the position of the cell relative to the stroma.

The cell changes seen around some cavities in the tumour masses appear to be due to necrosis and there is evidence that the tumour cells immediately beneath the epidermis degenerate as the masses grow down into the dermis. This degeneration may be caused by a deficient blood supply, but it is equally possible that tumour cells have a limited life span and that in older areas they die behind the advancing tumour edge. It is hard to imagine that the pedicles which connect the superficial tumour masses to the epidermis disappear through ischaemia whilst the epidermis and the masses themselves remain viable.

Madsen (1941) suggested that degeneration of tumour masses due to ageing occurs in superficial basal-cell carcinoma.

Necrosis is not the only cause of cavity formation because in some areas transitions from piecemeal invasion and enclosure of connective tissue to multiple small spherical cysts can be seen. In this case, altered stroma modifies the internal architecture of the tumour. The presence of stromal canals running through tumour masses is a feature which must be taken into account in interpreting the histological appearances of these tumours.

The incorporation of sweat ducts and pilosebaceous follicles in tumour masses does not result in their immediate complete destruction. They remain as hollow keratinized columns whose identity can only be recognized by the presence of a hair shaft, or by establishing their continuity with those parts of the organs beneath the growth. These keratinized columns may appear to be areas of ductlike differentiation in thin sections of a tumour, and in these preparations proof of their true nature may be impossible.

Perhaps the most striking fact to emerge from the split preparations is the perfect separation that occurs between the tumour and its stroma. This is a further point in favour of the idea that a state of near equilibrium exists at the palisaded margin of masses. The fine fibrous membrane which invests expansive masses once they invade the dermis and which can be stripped off the upper surface of the masses, is tangible evidence of the dermal barrier. At times the interlobular septa of the stroma come away with the surface membrane. The split preparations show the epidermal origin of the tumour much more clearly than the thick sections and the architectural details are essentially similar.

Outgrowths from the pilosebaceous follicles.—These structures seem different from the basal-cell carcinoma itself. Though composed of strands of cells they are not in any sense invasive. They are contained by a fibrous capsule which is denser and thicker than that which develops around the tumour masses. Even within the tumour area their dimensions are strictly limited, and no transitions are seen between outgrowths and basal-cell carcinoma. There is a remarkable uniformity of their structure. They are distinct from the " collars " which Zimmermann (1935) described on some vellus hair follicles and whose appearance in thick sections has been previously noted (Sanderson and Thiede). They differ also from the bulge (*Wülst*) of the hair root. Their whole appearance is suggestive of the early stages of epithelioma adenoides cysticum but more evidence is needed to support this idea. They are without doubt neoplastic and multifocal.

Practical implications.—It is common knowledge that the majority of basal-cell carcinomata are relatively benign in their behaviour. Some tumours may remain almost unchanged for years, others progress very slowly and expand into rather than invade the tissue around them. From a biological point of view these tumours exist in near equilibrium with their host. To the pathologist

this equilibrium is shown by marginal palisading of the tumour cells and a stromal membrane of fine fibrils. Between the tumour and the stroma there is a plane of cleavage. These facts justify treatment by local curettage which has been used by many people over the years, and which has recently been advocated most persuasively in his Dowling Oration by Sweet. However, the finding of strands of tumour arising from expansive masses and invading between the collagen bundles should lead to some caution in applying this method. Extensive invasive strands are found in the tenebrant type of basal-cell carcinoma and these are particularly dangerous when they spread to the loose periorbital connective tissue, or reach periosteum. It is obviously important to determine the histological character of a tumour before undertaking any form of treatment. The biopsy should include the deepest part of the tumour and its stroma.

The very diverse pattern of growth shown by the tumour cut in thick sections emphasizes the difficulty in subdividing basal-cell carcinoma. Most classifications depend upon the assumption that the histological pattern is more or less uniform throughout the tumour. A proper examination of sections shows that this assumption is false for the majority of tumours and the ready transition from solid islands to invasive strands and *vice versa* disposes of the idea that the type of cell differentiation determines the type of tumour to the degree that the classifications of Foot (1947) or Lever (1948) would suggest. The presence of pigment within tumours appears to be of little significance, although Madsen's statement that the majority of superficial lesions are pigmented is interesting.

It is perhaps worth while to point out that the examination of thick sections is only fruitful when there is sufficient transparent connective tissue around the structures examined to show their outlines clearly. Tumours which invade in compact masses or which are surrounded by considerable inflammatory infiltrate are unlikely to be of much use. The superficial variety of basal-cell carcinoma is therefore particularly suited to this method of examination.

Summary.

Thick sections of superficial basal-cell carcinoma show a variety of architectural patterns. At the margin, multiple buds develop from the epidermis. These coalesce and enlarge as they grow down and their connections to the epidermis become less numerous. The tumour also arises from the tips of the rete ridges in small areas and expands into the dermis in a honeycomb fashion. Nearer the centre, rounded masses are attached to the epidermis which has become thin and lost its rete ridges.

The central part of the tumour shows three particular patterns. There are expansive masses, which may be round, mulberry-like or lobulated. These have a margin of palisaded columnar cells and the stroma around them is fibrillar and rarefied. Invasive strands and membranes of flattened cells penetrate

between the connective tissue bundles. Piecemeal invasion and enclosure of connective tissue elements occur at the edge of some masses. The enclosed connective tissue appears to be transformed into multiple small cysts. The origin of the tumour from pilosebaceous follicles and sweat ducts is demonstrated. Circumscribed rounded masses composed of thin strands of cells surrounded by a band of thickened connective tissue arise from some pilosebaceous follicles in the skin around the tumour.

Split-skin preparations show that islands of basal-cell carcinoma attached to the epidermis separate clearly and leave indentations in the dermal surface. In places small multifocal buds fron the epidermis are seen. The dermal portion contains tumour masses, whose outer surface is separated from the epidermis by a thin tough membrane, which can be stripped cleanly off the surface of the buried tumour.

The sections were cut and stained by Mrs. Helga Thiede. I am grateful to Mr. R. J. Lunnon, F.R.P.S., for assisting with the photography, and to Miss A. Gretener for drawing Fig. 7. Mr. R. Hunter and Dr. H. J. Wallace have kindly allowed me to report their cases.

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